REMARKS/ARGUMENTS:

This Application is currently under final rejections. A prompt reconsideration of this Application is therefore respectfully requested.

Claims 1-2 and 17-32 remain in this application. Claims 3-9 have been previously canceled. Claims 10-16 have been previously withdrawn.

In the final office action dated June 4, 2003, claims 2, 18, 20-26, and 28-32 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Claims 1-2 and 27-29 are rejected under 35 U.S.C. §102(b) as being anticipated by Guengerich et al, U.S. Patent No. 5,886,157 (hereinafter as "the '157 patent"). Claims 1-2 and 17-29 are rejected under 35 U.S.C. §102(b) as being anticipated by Shade et al., WO00/62769 (hereinafter as "the WO'769 patent").

Applicants also acknowledge safe receipt of the "Notice of References Cited" (form PTO-892) and the attached references.

In response to these rejections, Applicants have amended claims 2, 18, 20, 24, 25, 27-30 and 32. Claims 2 and 29 have been amended to delete the compound α-naphthoflavone. As shown on page 22, lines 1-4 and page 28, lines 6-8, α-naphthoflavone is not among the most preferred compounds for inhibiting the dermal CYP1A and liver CYP1A enzymatic activities, respectively, although without doubt, it does have significant inhibitory effect on both the dermal CYP1A and liver CYP1A enzymatic activities. See e.g., Table 1 of the present invention. The deleting of α-naphthoflavone, therefore, is to correct inadvertent mistakes and should not be construed as narrowing the claims. Claims 18, 20, 24-25, 27-30 and 32 have been amended to further clarify the meaning of these claims. In addition, Applicants have amended the specification to correct "CYP1A" to –CYP1A1--, due to inadvertent mistakes. No new matter has been introduced.

Applicants respectfully submit that the amendment have overcome the rejections for reasons set forth below:

Claim rejections under 35 U.S.C. §112, second paragraph

Claims 28-32 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for lacking antecedent basis. Claims 18, and 20-26 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to further limiting the scope of claims.

In response to these rejections, Applicants have amended the claims to correct antecedent mistakes and further clarify the claims as follows:

Claims 28-32:

With regard to claim 28-29, Applicants have amended claims 27 to change the "dermal cytochrome P450 (CYP1A)" and "said inhibitor" to --dermal cytochrome P450 1A (CYP1A)-- and --said dermal CYP1A inhibitor--, respectively; claim 28 to change the "said dermal CYP1A inhibitor" to --said liver CYP1A inhibitor--. "Hepatic" is the adjective of "liver." In addition, claim 29 has been amended to change "said hepatic CYP1A" to --said liver CYP1A inhibitor--. Claim 30 has been amended to change "said liver CYP1A" to --said liver CYP1A inhibitor--. As set forth in the preamble of each claim or the previous claim it depends upon, after the amendments, it is clear that claim 27 claims a dermal CYP1A inhibitor and claims 29-30 claim a liver CYP1A inhibitor.

Claims 18 and 20-26:

The Examiner alleges that it is not clear how "a first[-pass] metabolism [sic] of a drug" or "conversion of a chemical into a carcinogen", as shown in dependent claims 20-24, and 25-26, can further limit the subject matter of the previous claims, i.e., claim 18. It appears that the Examiner is probably not familiar with the term "first-pass metabolism" in the pharmaceutical field, while in fact this is a term of art which is well-known in the field, particularly in determining the bioavailability of a drug, i.e., the effectiveness of a drug in the blood stream. It refers to the process of drug degradation within the body, whether it is taken up by oral administration, injection, or topical treatment, as described in the "Background" section of the present invention. Due to this metabolism, the bioavailability of the drug is affected, i.e., if the drug is degraded to a metabolite which no longer has the therapeutic effect, the effectiveness of the drug is abolished.

In response to these rejections, Applicants have amended claim 18 to clarify that it is the pharmaceutical composition of the present invention that inhibits the CYP1A enzymatic activities. A CYP1A, as disclosed in the Background section of the present application, has at least two enzymatic activities. As described in the amended claims 20 and 25, respectively, one of the CYP1A enzymatic activities is to perform a first-pass metabolism of a drug when such

drug is applied to the skin of a mammal. See Claim 20; See also page 2, lines 10-13 and 20-21, and page 7, lines 11-18. The other CYP1A enzymatic activity is to convert a chemical into a carcinogen when such chemical is in contact with the skin. See Claim 25; See also page 3, lines 1-4, and page 4, lines 14-15. These two activities are distinct, with the former being affecting the therapeutic effects and side effects of a drug (page 2, lines 15-16), and the latter being enhancing a chemically induced carcinogensis in animals and in humans (page 3, line 4).

In view of aforementioned, there is no doubt that the amended claim 18 claims a pharmaceutical composition that comprises a dermal CYP1A inhibitor which inhibits a dermal CYP1A enzymatic activity. Claim 20 further limits the pharmaceutical composition of claim 18 to inhibition of one of the dermal CYP1A enzymatic activities, i.e., the first-pass metabolism of a drug, when this drug is applied to the skin of a mammal. Claim 25 further limits the pharmaceutical composition of claim 18 to inhibition of the conversion of a chemical into a carcinogen when this chemical is in contact with the skin of a mammal. Thus, there is no question that claims 20 and 25 each claims a subgroup of the subject matter of the amended claim 18, and further limits the scope of the amended claim 18.

With respect to claims 21-24 and 26, the specification and claims as originally filed defines the word "drug" (page 7, lines 14-21, and page 8, lines 1-3), which encompasses a wide range of compounds. It is well known in the art that a dermatological drug (see original claims 5-7 and 11) is a subgroup of drug that treats diseases related to the skin. Retinoid, retinoic acid and retinoid-like compounds are examples of dermatological drugs (page 8, lines 5-8 and 14-21, and page 9, lines 1-8). Retinoid, retinoic acid and retinoid-like compounds also exert therapeutic effects on other diseases (page 9, lines 8-21, and page 10, lines 1-7). Thus, there is no question that each of claims 21-23 further limits the scope of the claim it is depending upon.

As to claim 24, topical co-administration of the drug (such as retinoid) and the pharmaceutical composition of the present invention (i.e., containing a CYP1A inhibitor) is certainly one application of the present invention, as opposed to other applications, such as administering the pharmaceutical composition and the drug concurrently but separately or sequentially. Thus, claim 24 certainly further limits the scope of the claims it depends upon. In addition, Applicants have amended claim 24 to add – an effective amount of – before "said pharmaceutical composition," to further clarify the claim as suggested by the Examiner.

As to claim 26, it is well known in the art that carcinogens cause cancers, and skin cancers are a subgroup of cancers and also a subgroup of skin diseases.

As aforementioned, claim 21 claims a subgroup of claim 20, claims 22-24 each claims a subgroup of claim 21, and claim 26 claims a subgroup of claim 25. Each dependent claim further limits the scope of the previous claim it depends upon. The relationship between the limitations and the subject matter of the previous claim has been well taught by the specification and the claim language.

Claim rejections under 35 U.S.C. §102(b)

Claims 1-2 and 27-29 are rejected under 35 U.S.C. §102(b) as being anticipated by the '157 patent. Claims 1-2 and 17-29 are rejected under 35 U.S.C. §102(b) as being anticipated by the WO'769 patent.

Applicants respectfully traverse the rejections.

Arguments Over Guengerich et al. U.S. 5,886,157 (hereinafter "the '157 patent)

The Examiner argues that "US'157 teaches a compound α-naphthoflavone as a cytochrome P450 1A (CY1A) inhibitor, **see claim 8**." (emphasis added). (See page 4 of the Office Action dated June 4, 2003).

Claim 8 of the '157 patent, however, does not recite α-naphthoflavone as a cytochrome P450 1A (CY1A) inhibitor. It reads as follows:

> "The method of claim 7, wherein the protein is selected from the group consisting of P450 1A2 and 1A1, and the inhibitory ligand is α-naphthoflavone." (emphasis added).

Claim 7 of the '157 patent recites as follows:

> "The method of claim 1, further comprising the step of adding a strong inhibitory ligand before adding the detergents to the fractionated cells." (emphasis added).

There is nothing in this claim connecting the inhibitory ligand to the inhibitory activity of CYP1A. In fact, if we trace claim 7 back to the independent claim 1, which recites as follows:

"A method of purifying a recombinant cytochrome P450 protein from a host cell culture comprising the steps of:

a. fractionating the host cells to prepare their membranes;

b. adding a non-ionic detergent in a concentration of between 0.8% to 2% (w/v) and in a detergent to protein ratio of between 4:1 to 10:1 to the membranes;

c. adding an ionic detergent in a concentration of between 0.4% to 0.8% (w/v) and in a detergent to protein ratio of between 2:1 to 4:1 to the membranes;

d. centrifuging the membrane detergent mixture to remove insoluble materials; ad,
e. purifying the protein in the following order:
i) through a diethylaminoethyl-beaded column;
ii) through a carboxymethyl-beaded column; and
iii) through a hydroxylapatite column.

One would know, by reading the specification and claims 7 and 8 of the '157 patent, that the inhibitory ligand is NOT and can NOT be a "CYP1A inhibitor." For example, in column 8, lines 62-67, and column 9, lines 1-7, the inventors of the '157 patent explains that "a strong inhibitory ligand, e.g., α-naphthoflavone (7,8-benzoflavone), may be added to the membranes before adding the detergents to the fractionated cells. This helps to stabilize the cells and to maintain catalytic activity." (emphasis added). This excerpt makes clear that the so-called "inhibitory ligand" is not to be meant "CYP1A INHIBITOR" or otherwise the catalytic activity of the CYP1A should be suppressed.

This is further supported by the results shown in Fig. 16 of the '157 patent and the accompanied text in the ""Brief Description of the Figures" section, which indicated that the effect of α-naphthoflavone is on the stability of recombinant P450 1A. With the addition of α-naphthoflavone, the enzymatic activity of CYP1A is equal or better than without α-naphthoflavone, which is opposite to the findings of the present invention.

The Examiner's argument of "inherency" is also misplaced. A new use of an old compound is well known to be patentable under 35 U.S.C. § 101. See also, Diamond v. Diehr, 450 U.S. 175 (1981) ("An application of a law of nature or mathematical formula to a known structure or process may well be deserving of patent protection"). Since the use of α-naphthoflavone as a CYP1A is not disclosed in the '157 patent and on the contrary, the '157 patent discloses that α-naphthoflavone cannot be a CYP1A inhibitor, there can be no "inherency" in this case.

Applicant would also like to draw to the attention of the Examiner with regard to the construction of the previously amended claim 1, where the "CYP1A inhibitor" is NOT a preamble but effectively a claim limitation. Claim 1 recites "a dermal cytochrome P450 1A (CYP1A) inhibitor, wherein said dermal CYP1A inhibitor is a compound selected from the group consisting of ..." Therefore, Applicants are not reciting an "intent use" of a compound but

rather, a definite use of the compound. In other words, Applicants have expressly and unequivocally claim the use of this compound as a dermal CYP1A inhibitor.

In addition, "anticipation under 35 U.S.C. § 102 requires that disclosure in a single piece of prior art of each and every limitation of a claimed invention." Electro med. Sys. S.A. v. Cooper Life Sciences, 34 F.3d 1048, 1052 (Fed. Cir. 1994). See also Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631 (Fed. Cir. 1987) ("[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference"). Since the '157 patent never discloses that α-naphthoflavone can be used as a CYP1A inhibitor and in fact teaches away from being able to be used as a CYP1A inhibitor, Applicants respectfully submit that Applicants' claimed invention is not anticipated by the '157 patent.

Arguments Over Shade et al. WO00/62769 (hereinafter WO'769)

The Examiner alleges that "WO'769 teaches a compound (i.e., β-naphthoflavone) and a composition containing β-naphthoflavone. WO'769 further teaches a topical composition containing β-naphthoflavoneas an effective active agent, **see claim 1-2**." (emphasis added).

As shown in claim 1, however, the topical composition referred to by the Examiner is for treatment of glaucoma or ocular hypertension. The compound that possesses this activity is an AP-1 activator. AP-1 , the Activator Protein-1, is is a dimeric gene transcription promoter comprised of subunit proteins which are the products of at least three different proto-oncogene families: the Jun(c-Jun, v-Jun, JunB, JunD), Fos (c-Fos, v-Fos, FosB, FosB2, Fra-1, Fra-2) or activating transcription factor (B-ATF, ATF2, ATF3/LRF1) families. See page 1, line 31-34 of WO'769. AP-1 is totally different from CYP1A. Thus, the use of β-naphthoflavone as an AP-1 compound can not be equivalent to the use of β-naphthoflavone as a CYP1A inhibitor.

In addition, as set forth in the arguments over anticipation of the '157 patent (*supra*), there is no "inherency" of the use of β-naphthoflavone as a CYP1A inhibitor. A new use of an old compound is clearly patentable under 35 U.S.C. § 101. Since claim 1 of the present invention makes clear that β-naphthoflavone is used as a CYP1A inhibitor and the CYP1A inhibitor is a limitation of claim, to the extent that WO'769 never discloses the use of β-naphthoflavone as CYP1A inhibitor, the present claimed invention is not anticipated by WO'769.

Applicants therefore respectfully request that the rejections over the '157 patent and WO'769 be withdrawn.

In view of the foregoing, the rejections have been overcome and the claims are in condition for allowance, early notice of which is requested. Should the application not be passed for issuance, the examiner is requested to contact the applicant's attorney to resolve the problem.

Respectfully submitted,

Fei-Fei Chao

Fei-Fei Chao, Ph.D.
Reg. No. 43,538

Date: August 19, 2003
Fei-Fei Chao, Ph.D.
Venable, Baetjer, Howard & Civiletti, LLP
1201 New York Avenue, N.W., Suite 1000
Washington, D.C. 20005
Tel.: (202) 216-8011

DC2DOCS#478548